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COMBINED CHONDROITIN SULFATE AND GLUCOSAMINE IS MORE EFFICIENT THAN CELEBREX IN REDUCING SERUM LEVELS OF COLL2-1, A CARTILAGE DEGRADATION BIOMARKER, IN PATIENTS WITH SEVERE OA: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, MULTICENTRIC CLINICAL TRIAL

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Purpose: To investigate soluble osteoarthritis (OA) biomarkers (Coll2-1, Coll2-1NO2 and Fib3-2) in the per-protocol (PP) population of the double-blind Multicentre Osteoarthritis interVEntion trial with Sysadoa (MOVES) comparing the symptomatic efficacy and safety of Chondroitin Sulfate (CS) plus Glucosamine Hydrochloride (GH) versus CElecoxib (CE) in patients with knee OA. Coll2-1 is a peptide located in the triple helical part of type II collagen and Coll2-1NO2 is the nitrated form of Coll2-1. Fib3-2 is a fragment of fibulin-3, an extracellular glycoprotein highly expressed in OA cartilage. The levels of these biomarkers have been found to be elevated in serum of OA patients and to vary with severity.
Methods: Coll2-1, mColl2-1NO2 and Fib3-2 were directly measured by immunassays (ARTIALIS SA, Liège, Belgium) in the serum of the PP population of the MOVES trial, which included 606 patients with knee OA receiving 400 mg of CS plus 500 mg of GH three times daily or 200 mg of CE once daily for 6 months. This PP population included 418 subjects (215 receiving CS+GH and 203 receiving CE) with at least one biomarker value at three time points (D0, D120 and D180).
Results: Serum biomarkers values at baseline or at follow-up D120 and D180 were not associasted with age, sex, race, weight, height of BMI. In overall PP population, there were no statistically significant differences between CE and CS + GH groups for any of the three biomarkers at baseline, D120 and D180. However, there was a trend in favor of CS+GH in reducing Coll2-1 at D180 ($p=0.069$) and a trend in favor of CE to reduce Fib3-2 ($p=0.055$). When population was stratified according the radiological OA severity, the occurrence of a swelling or effusion event, the WOMAC score or the sympromatic response to treatment some significant differences in biomarkers serum levels were observed between treatment groups. At D180, CS +GH induced a significantly greater decrease of Coll2-1 in the subgroups of patients with the more severe radiographic disease (K&L III), with synovitis (at least one joint swelling or effusion event, in OMERACT-OARSI responders or in patients with WOMAC pain at baseline $\leq$ 369 compared to CE ($p<0.05$). For Coll2-1NO2, there was a trend in favor of CS + GH in the sub-population having at least one joint swelling event during the study period ($p=0.077$) at D180. In addition, CE was more effective than CS + GH in reducing Fib3-2 at D180 in patients with WOMAC pain at baseline > 369 ($p=0.042$).
Conclusions: CS + GH was more efficient than CE in reducing serum Coll2-1, a marker of type II collagen degradation. This data indicates that CS + GH may down-regulate cartilage catabolism, particularly in a subgroup of patients with severe OA. These results are in accordance with the symptomatic benefits observed in the clinical trials with these therapies.

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ASSOCIATIONS OF SERUM BIOMARKERS WITH RESPONSE TO SPINAL PROCEDURES IN SUBJECTS WITH AXIAL LOW BACK PAIN

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Purpose: Despite increasing numbers of interventional procedures being performed for axial low back pain, selection criteria remain unclear and outcomes suboptimal. Serum biomarkers represent a potential opportunity to improve clinical ability to predict response to treatment and provide insight into mechanisms of action of procedures such as spinal injections. The purpose of this study was to examine the association of serum biomarkers with pain and pain related disability in individuals with axial low back pain undergoing different spinal procedures.
Methods: Consecutive patients 18 years or older were recruited from academic medical center departments of Physical Medicine and Rehabilitation and Anesthesiology who had already consented for either epidural steroid injection (ESI, n=48) or medial branch block without steroid (MBB, n=45) as part of their routine clinical care. Subjects were eligible if they had primarily axial low back pain that was more severe than pain in any other part of the body, and did not have radiation of pain into the lower extremities, red flags of serious underlying illness (such as fever, weight change, bowel or bladder changes or neurologic decline), recent oral steroids, uncontrolled psychiatric illness, or systemic inflammatory conditions.
Serum blood samples were taken immediately prior to the procedure and at clinical follow-up and assayed for Neuropeptide Y, E-selectin, RANTES, CS846, CTXII, and serotonin. Responders to injection were defined as improvement in pain score of 2 points or more on a 0-10 numeric pain rating scale (immediately following the procedure for MBB, and at follow-up for ESI). Gender, age, race, education, employment status, smoking status, Oswestry disability index, Roland Morris Disability, McGill Pain Questionnaire, Generalized Anxiety, PHQ-9, walking speed, fear avoidance beliefs, catastrophizing, cumulative illness rating scale, prior treatments and exercise, treatment expectation, and medications were also collected. Wilcoxon rank sum and Fisher's exact tests were used for comparing responders and non-responders.
Results: Response rates were 78% and 48% for MBB and ESI, respectively. Among subjects undergoing MBB, responders had higher baseline RANTES levels than non-responders ($p=0.04$). Among subjects undergoing ESI, responders had lower baseline CS846 levels ($p=0.04$), greater frequency of past exercise ($p=0.04$), and greater percentage expecting relief ($p=0.04$) than non-responders. No other associations were observed with other baseline clinical variables.
Among subjects undergoing MBB, serotonin concentrations increased pre- to post-procedure in non-responders and decreased in responders (responder to non-responder difference $p=0.048$). Among subjects undergoing ESI, E-selectin showed a tendency toward more decreased levels post-procedures in responders ($p=0.1$).
Conclusions: These data identify candidate serum biomarkers that may have utility for patient selection for spinal procedures. Because clinical decision making for interventional management for axial low back pain is even more challenging than for radiculopathy, these represent important biomarkers for use in prospective studies to assess and validate their predictive ability. In addition, the associated biomarkers may provide useful insight into the mechanism of spinal procedures by identifying important targets for future study. Larger studies are needed to confirm the utility of these identified biomarker candidates.

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IDENTIFICATION AND CLINICAL CHARACTERIZATION OF BIOMARKERS DESCRIBING JOINT INFLAMMATION

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Purpose: A proportion the osteoarthritis (OA) patients experience joint inflammation with associated pain and discomfort. However to present day, there are limited objective measures available for monitoring and identify those patients who have inflammatory OA. The aim of this study was study the association between joint inflammation and biomarkers associated with connective tissue inflammation and cartilage degradation. We used four biomarkers that have previously been shown to be associated with inflammation and joint destruction.
Methods: Biomarkers were measured in 288 women and 186 men with OA and mean age of 64.2 year (SD 7.6) from the VIDEO cohort. Knee effusion, clinical signal of synovitis and WOMAC pain, stiffness and function, and ESR were recorded for each patient. Serum levels of the connective tissue biomarkers C3M and CRPM (type III collagen and C-reactive protein neo-epitopes, Nordic Bioscience), urinary CTX-II/creatinin [IDS PLC] (type II collagen neo-epitopes) and serum COMP